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The Clinical Pharmacology of Tolmesoxide

A New Vasodilator Antihypertensive Agent

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Summary. The haemodynamic response and pharmacokinetics of single dose oral tolmesoxide were studied at various dose levels in 4 patients with severe hypertension. There was a reproducible fall in mean arterial pressure from baseline of 24.2% and a rise in heart rate of 37.6% following administration of tolmesoxide. The onset of antihypertensive action occurred within 1 h, with a peak effect at 3 h after dosing. The mean duration of action was up to 12.0 h. Tolmesoxide had a mean half-life of 3.0 h. It was rapidly absorbed with a mean peak plasma level occurring at 1.0 h. Plasma levels correlated well with the doses administered. Side-effects included mild nausea, facial flushing and postural symptoms.

Key words: tolmesoxide, vasodilator, hypertension; pharmacokinetics, haemodynamics, plasma renin activity

Vasodilators have an established role in the treatment of hypertension (Chidsey and Gottlieb 1974), although the available agents are not without clinically significant adverse effects. Tolmesoxide ([4,5 dimethoxy – 2 methylphenyl] methyl sulphoxide), a new vasodilator agent, is a member of the sulphoxide group of drugs and is chemically dissimilar from existing vasodilators (Fig. 1). We studied the efficacy and safety of acute oral dosing with tolmesoxide in patients with severe hypertension.

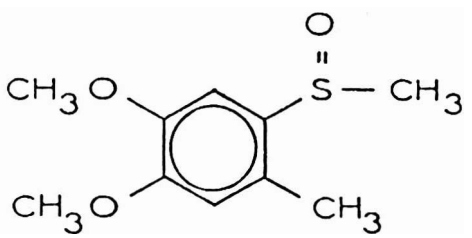
Patients and Methods

Four drug-free patients with essential hypertension whose mean age was 59 years (range 50–68 years) entered an open, dose-finding, single-blind study of tolmesoxide. All patients were admitted to hospital 2 days prior to the study. The protocol was approved by the hospital ethics committee and written informed consent was obtained from the patients.

Placebo Phase

On 4 successive days patients received 100 mg, 200 mg, 400 mg and 600 mg tablets of placebo tolmesoxide. On each day supine and standing blood pressure and heart rate were measured prior to administration of the placebo and 1, 2, 3, 4, 6, 8, 12 and 24 h after administration.

On the fourth placebo day blood samples for measurement of plasma renin activity were taken supine and while standing following exercise for 1 h. Blood samples were also taken for blood sugar and serum insulin levels while fasting and 1.5 h post-prandial. Baseline renal and liver function were assessed by blood urea and serum electrolytes, creatinine, bilirubin, GOT, GPT, alkaline phosphatase and proteins. An electrocardiograph was done on the final placebo day.



TOLMESOXIDE

Fig. 1. Structure of tolmesoxide

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Table 1. Comparison of supine blood pressure readings over 4 placebo days

Blood pressure	Day 1	Day 2	Day 3	Day 4
Systolic	209 ± 7.4	204 ± 6.9	200 ± 6.0	202 ± 8.2
Mean	154 ± 2.6	150 ± 3.3	147 ± 4.4	149 ± 4.2
Diastolic	126 ± 1.4	123 ± 2.8	122 ± 4.9	122 ± 3.3

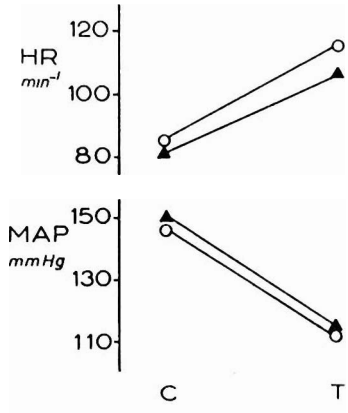

Fig. 2. Mean arterial blood pressure (MAP) and heart rate responses to tolmesoxide following the initial effective dose (O——O) and the confirmatory dose (▲——▲). (Values are means ± SEM, $n = 4$, C – control, T – tolmesoxide)

Active Phase

Following the placebo phase, patients entered the active dose-finding phase in which they received single oral doses of 100 mg, 200 mg, 400 mg and 600 mg of tolmesoxide while fasting on successive days until a significant response was achieved, as defined by a fall in diastolic blood pressure (DBP) (phase V) greater than 15%, or until the maximum dose was reached. In order to confirm the haemodynamic response, the initial effective dose was repeated on the following day and will be referred to as the confirmatory dose. Only patients with DBP greater than 105 mm Hg were admitted to the dose-finding part of the study.

On each day of the active phase supine and standing heart rates and blood pressures were measured as during the placebo phase. All blood pressure readings were recorded by one observer using a Hawksley random-zero sphygmomanometer. Mean arterial pressure (MAP) was calculated as one third pulse pressure plus diastolic pressure. Student's *t* test for paired data was used for comparison of results. Blood samples for assay of tolmesoxide and its major metabolite (4,5 – dimethoxy – 2 – methyl), phenylmethyl sulphone, were withdrawn at 15, 30 and 45 min and at 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after administration of each dose of tolmesoxide including the confirmatory dose. Daily blood samples for estimation of blood sugar and serum insulin were withdrawn while fasting and postprandial as on the placebo phase. Blood samples for plasma renin assay were taken following the maximum antihypertensive response to the initial effective and confirmatory doses of tolmesoxide. On each day of this phase electrocardiographs were recorded prior to administration of tolmesoxide and 2 h after administration. At the end of the study renal and liver function were re-assessed.

Assay of Tolmesoxide

Plasma concentrations of tolmesoxide and its major metabolite were measured by high pressure liquid chromatography, using a method similar to that of Lloyd-Jones et al. (1981). To 1.0 ml samples of plasma were added 0.1 ml of water containing 50 µg/ml internal standard – (4,5 – dimethoxy – 2 – isopropyl) phenylmethyl sulphoxide. Samples were extracted twice with 5.0 ml of ether. The pooled solvents were evaporated at 40 °C under nitrogen and were reconstituted with 0.1 ml mobile phase prior to chromatography. A Pye-Unicam model LC3 liquid chromatograph fitted with a Rheodyne sample valve (20 µl loop) was used with the column eluant monitored at 240 nm. The column was stainless steel 25 cm × 0.25″ o.d. packed with Spheriserb 5 ODS. The mobile phase was 60/40 methanol/water at a flow of 1 ml/min. Blank samples of plasma, to which had been added various concentrations of tolmesoxide and its major metabolite, were included with each batch to provide a calibration line.

Results

Within patients there was no significant difference in the mean 24 h values of MAP while on placebo. The mean MAP in mm Hg for the 4 placebo days varied from 147 ± 4.4 SEM to 154 ± 2.6 SEM. Systolic pressure (SBP) ranged from 200 ± 6.0 SEM to 209 ± 7.4 SEM and diastolic pressure (DBP) from 122 ± 4.9 SEM to 126 ± 1.4 SEM (Table 1).

The mean maximal fall in MAP in response to the 'effective dose' of tolmesoxide was 36 mm Hg from a control value of 149 mm Hg ($p < 0.005$) (Fig. 2) – a fall in mean blood pressure of 24.2% from baseline. The mean maximal fall in response to the confirmatory dose of tolmesoxide was 35 mm Hg from a control value of 150 mm Hg (23.3%) $p < 0.001$). These responses in blood pressure were associated with a mean rise in heart rate of 32 beats/min on the effective dose and of 24 beats/min on the confirmatory dose (Fig. 2). The effective dose of tolmesoxide ranged from 200 mg to 600 mg.

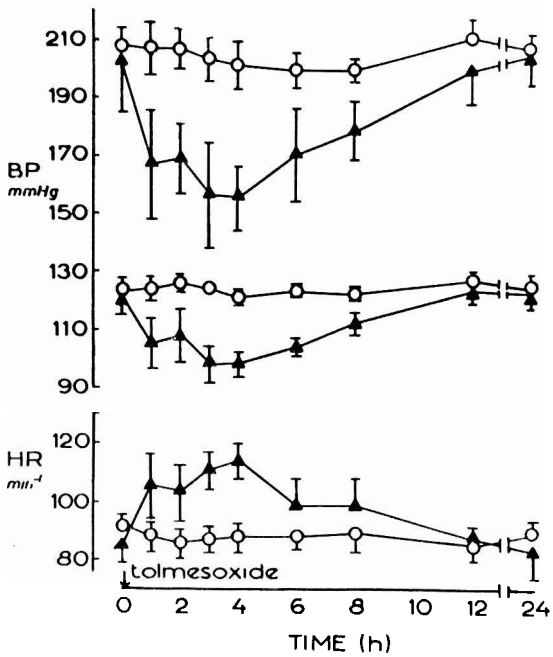

Fig. 3. Time course of blood pressure and heart rate responses to tolmesoxide (▲——▲) compared with the means for the 4 placebo days (O——O)

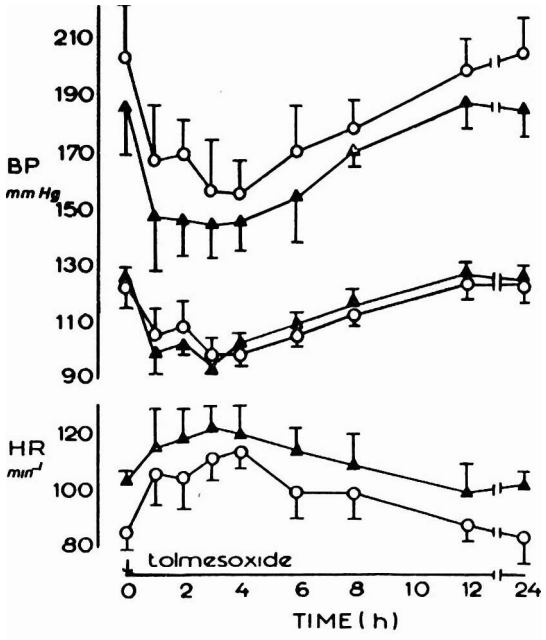

Fig. 4. Comparison of supine (O——O) and standing (▲——▲) blood pressures and heart rates following the effective dose of tolmesoxide

The blood pressure and heart rate responses to the effective dose of tolmesoxide are compared with the control values for the 4 placebo days in Fig. 3. The onset of action occurs within one hour of drug administration with a fall in both SBP and DBP and an increase in heart rate. The maximum response occurs at 3 to 4 h with falls of 48 and 25 mm Hg in the mean SBP and mean DBP respectively and a rise in heart rate from a mean of 88 to 114 beats/min. The duration of action was up to 12 h. The increase in heart rate closely follows the fall in pressure.

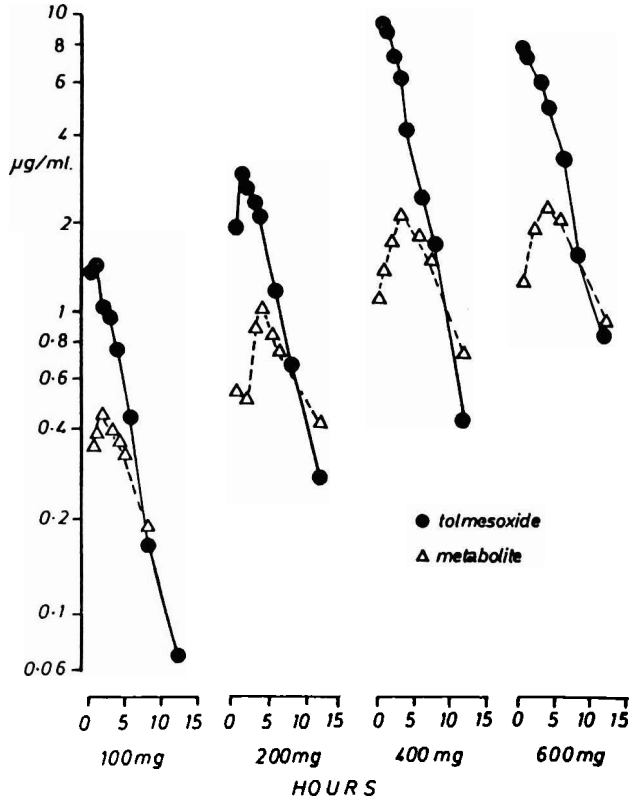

Fig. 5. Plasma concentrations of tolmesoxide (●) and its major metabolite (△) in a patient who received 100 mg, 200 mg, 400 mg and 400 mg of tolmesoxide on successive days

The effect of posture on the response to tolmesoxide is shown in Fig. 4. The mean baseline supine and standing SBP were 203 ± 18.3 and 185 ± 16.3 mm Hg respectively, the corresponding values after tolmesoxide being 169 ± 12.4 and 144 ± 12.4 mm Hg. These figures represent a fall in baseline SBP of 18 mm on standing and of 25 mm Hg following tolmesoxide. This postural fall is no greater than the postural variation over 24 h for the mean of the 4 placebo days. However, 1 patient had a fall in SBP from 116 mm Hg lying to 90 mm Hg on standing and experienced postural symptoms (see below).

The mean baseline supine and standing plasma renins were 4.6 ± 1.7 and 5.3 ± 2.1 ng/ml/h. The corresponding values following the effective dose of tolmesoxide were 6.8 ± 2.9 and 8.0 ± 3.4 ng/ml/h and following the confirmatory dose were 8.5 ± 3.7 and 6.9 ± 4.0 ng/ml/h. Baseline fasting and post-

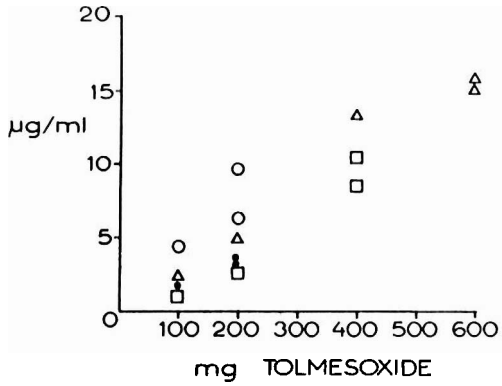

Fig. 6. Peak tolmesoxide concentrations as a function of dose. Initial and confirmatory doses are included and each patient is represented by a different symbol

prandial blood sugars were normal and there was no significant rise in blood sugar following administration of tolmesoxide. Although the mean post-prandial serum insulin fell from 71.2 ± 23.6 to 45.0 ± 7.5 μg/l following the initial effective dose of tolmesoxide, the postprandial serum insulin was at least double the level of the fasting serum insulin after administration of each dose of tolmesoxide in all patients. There was no significant change in hepatic or renal function or in electrocardiographs from baseline assessment.

Fig. 5 shows plasma concentration of tolmesoxide and metabolite as a function of time in a representative patient who received 100 mg, 200 mg, 400 mg and a confirmatory dose of 400 mg. Tolmesoxide was rapidly absorbed in all patients and peak concentrations were observed at between 15 min and 1 h after drug administration. There was a good relationship between the maximum observed concentration of tolmesoxide and the dose administered (Fig. 6). The mean half-life of tolmesoxide was 2.9 ± 0.25 h (range 2.0–3.7 h). Amounts of metabolite in plasma were measurable at 30 min and peak concentrations were observed at 2–4 h. As for the parent drug, there was a good relationship between peak plasma concentrations and dose of tolmesoxide.

Side-effects were minimal and not reproducible in every case with the confirmatory dose. One patient experienced facial flushing 30 min following administration of tolmesoxide in a dose of 400 mg and this lasted 15 min. This patient also experienced severe nausea lasting 3.5 h at the same dose but following the confirmatory dose the nausea was mild and transient. Nausea was experienced by one other patient at a dose of 200 mg but was mild and lasted 30 min following the initial effective and confirmatory doses. Headaches and palpitations were also experienced by this patient and lasted up to 2.5 h. The former patient complained of postural dizziness following the initial effective dose and his symptoms coincided with a postural fall in blood pressure of 26 mm Hg.

Discussion

Studies in rats indicate that tolmesoxide lowers blood pressure by a direct relaxant effect on vascular smooth muscle (Doxey 1978). Collier et al. (1978) have shown that tolmesoxide is approximately equipotent in dilating arterioles and noradrenaline constricted veins. Thus, tolmesoxide should be classified as a non-selective vasodilator (O'Malley et al. 1980). The hypotensive effect of tolmesoxide in normal volunteers has been documented by Buylla et al. (1979) who showed a fall in standing systolic pressures. Our findings also showed a pattern of response consistent with non-selective vasodilation. The fall in mean SBP and DBP in the present study was marked and reproducible and could not be attributed to a hospitalisation or placebo effect as there was no significant fall in mean blood pressure over the 4 placebo days. The rise in heart rate which closely followed the fall in SBP and DBP, and the rise in plasma renin are consistent with the reflex haemodynamic effects documented with other vasodilators (Freis et al. 1953; Ueda et al. 1968). Side effects which occurred in 2 of the patients were not of sufficient severity of warrant withdrawal from the study and were less severe or absent with the confirmatory dose.

Tolmesoxide, in common with other vasodilators (Lowenthal et al. 1978; Reidenberg et al. 1973), has a short half-life, probably due to rapid metabolism as indicated by the early appearance of the major metabolite in the plasma. However, the relatively long duration of action (up to 12 h) contrasts with the short half-life and suggests that tolmesoxide has a specific mechanism of action of relatively long duration in the vascular walls in a manner suggested for hydralazine (Moore-Jones and Perry 1966) and minoxidil (Pluss et al. 1972).

In conclusion, our results suggest that tolmesoxide is an effective antihypertensive agent in single oral doses up to 600 mg. The pharmacokinetic pattern is similar to that observed with over vasodilators and the haemodynamic response is consistent with non-selective vasodilation. The efficacy and safety of tolmesoxide should be further studied in chronic dosage.

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